

Folic acid: a public-health challenge

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Despite worldwide public-health campaigns recommending periconceptional daily supplementation of synthetic folic acid to reduce the risk of neural tube defects, many women are not following these recommendations. At the same time, in most European countries no decline in defects has been recorded in recent years. Vulnerable groups are those with a low standard of education, young people, and women with unplanned pregnancies. Furthermore, in most countries without mandatory fortification, the general population is not consuming the recommended 0.4 mg of food folate per day. Voluntary fortification improves the situation, but does not reach all parts of the population. In the USA, Canada, and Chile, mandatory fortification of flour substantially improved folate and homocysteine status, and neural tube defects rates fell by between 31% and 78%. Nevertheless, many countries do not choose mandatory folic acid fortification, in part because expected additional health benefits are not yet scientifically proven in clinical trials, in part because of feared health risks, and because of the issue of freedom of choice. Thus, additional creative public-health approaches need to be developed to prevent neural tube defects and improve the folate status of the general population.

There is general consensus that folic acid supplementation during the periconceptional period substantially reduces the risk of neural tube defects. This reduction in risk has led many health organisations to issue recommendations for women to take 0.4 mg of synthetic folic acid daily in addition to consuming food folate from a varied diet.¹ Three public-health strategies exist for reaching the recommended daily dose required for effective prevention of defects: (1) women take supplements with folic acid in combination with a healthy diet; (2) foods are fortified with synthetic folic acid on a voluntary basis; and (3) a staple food is fortified on a mandatory basis. After a short overview of the preventive potential of folic acid the main aim here is to review successes and failures of these three methods. Special emphasis is placed on population-based public-health interventions to prevent neural tube defects at the level of communities and nations. Of particular interest are results published after mandatory fortification has been introduced in several countries. The folate

status of the general population in various countries will also be discussed.

Folate is the generic term for this water-soluble B-complex vitamin. It functions as a coenzyme in single-carbon transfers in the metabolism of aminoacids and nucleic acids. Folic acid (pteroylmonoglutamic acid, or PGA) is the most oxidised and stable form of folate. It is the form used in vitamin supplements and in fortified food products. Most naturally occurring folates, called food folate, are pteroylpolyglutamates. Dietary folate equivalents adjust for the nearly 50% lower bioavailability of food folate compared with that of synthetic folic acid (PGA) (panel 1).¹ Folic acid plays an important part in the prevention of neural tube defects and is suspected to prevent some other congenital anomalies and low birthweight,² as well as chronic diseases such as cardiovascular disease, cerebral stroke, cancer of various sites, depression,³ dementia,⁴ and osteoporosis.^{5,6} Definite scientific evidence of a risk reduction in clinical trials is only available for synthetic folic acid and neural tube defects.

Panel 1: Dietary folate and synthetic PGA equivalents

1 µg of dietary folate equivalent=0.6 µg of folic acid (PGA) from fortified food or as a supplement taken with meals=1 µg of food folate=0.5 µg of synthetic PGA taken on an empty stomach.

Effect of folic acid on risk of anomalies and disease

Two of the most common serious birth defects of the brain and spine are spina bifida and anencephaly. These neural tube defects occur when part of the neural tube, which later develops into spinal cord and brain, does not close. Closing normally happens around 24 days after conception—ie, before the woman has realised that she is pregnant. In the case of anencephaly all infants are stillborn or die shortly after birth, whereas in the case of spina bifida, children survive with lifelong disabilities including paralysis, bowel and bladder incontinence, and other physical handicaps despite extensive medical and surgical care.⁷ Spina bifida prevalence is determined by time, region, and ethnicity.⁸ Since prenatal diagnosis leads to the termination of a pregnancy in many cases, estimation of prevalence is difficult, especially in countries without national registration of pregnancy terminations due to neural tube defects. The main risk factors are a

Search strategy and selection criteria

This review is a non-systematic overview of articles published in English, German or French over the past decade. Thus, main emphasis is placed on results from western countries. Several earlier, commonly referenced, key publications are also cited. Unpublished findings presented in press releases were not considered. Articles were selected from the personal bibliographic databases of the authors and from a MEDLINE search with more than 40 key words including "folic acid", "neural tube defects", "awareness", "supplementation", "fortification", "safety", "masking B12-deficiency", "twinning rates", "cardiovascular disease", "cancer", "congenital malformation", and "genetic selection".

previous affected child or fetus, inadequate maternal intake of folic acid, diabetes, use of valproic acid or carbamazepine, obesity,⁹ and impaired vitamin B-12 status.⁸ Results of intervention studies^{10–12} have shown that periconceptional use of supplements with folic acid alone, or multivitamins combined with folic acid, can lower the risk of neural tube defects by 40% to 80%. At present, primary prevention is only possible through folic acid supplementation and fortification.

More and more evidence suggests that folic acid prevents other major birth defects.^{13–15} In a randomised clinical trial,¹⁶ periconceptional multivitamin supplementation resulted in a 47% reduction of birth defects other than those in the neural tube. Results of observational studies showed fairly consistently an inverse association between maternal use of multivitamins with folic acid and risk of congenital heart defects and orofacial clefts.^{13,15} The randomised clinical trial¹⁶ provides the strongest evidence that multivitamins prevent congenital heart defects. For the prevention of oral clefts, a higher dose of folic acid is probably necessary.¹⁴ Multivitamin supplement use is also inversely associated with anomalies of the urinary tract and with limb defects.¹³ In relation to folic acid alone, a reduced risk of anus imperforatus was described among women using folic acid in China.¹⁷ There is some preliminary evidence that abnormal maternal folate metabolism may contribute to the formation of fetal trisomy 21.^{18,19} For most of the mentioned congenital anomalies there are also studies that do not suggest an inverse association with folic acid and multivitamins, and some of the evidence is mainly based on case-control studies.¹³

A raised plasma homocysteine concentration is an independent risk factor for cardiovascular disease and stroke.²⁰ Folic acid in cooperation with vitamin B12 lowers plasma homocysteine concentrations. Data from several but not all prospective studies showed a reduced risk of cardiovascular disease²¹ and stroke²² associated with high folate intake or blood concentrations. However, randomised clinical trials have not yet provided evidence that reducing homocysteine concentrations by improvement of folate status is effective in the primary prevention of cardiovascular diseases. Results of trials in recurrent cardiovascular disease have been inconsistent.^{23–25} In the Vitamin Intervention for Stroke Prevention trial,²³ for example, folic acid, vitamin B6, and vitamin B12 had no effect on subsequent stroke, coronary heart disease, and death in patients with non-disabling cerebral infarction, but survival was improved in a subgroup of patients who were not already taking B12 supplements and did not have B12 malabsorption or renal failure.²⁶ Several randomised clinical trials are still in progress and should—in the context of a meta-analysis—have adequate statistical power to provide evidence of the relevance of folate and vitamin B12 for cardiovascular disease.^{27–29}

The results of observational studies consistently show an inverse association between folate intake or blood

concentrations, or both, and the frequency of colorectal carcinomas, and less clearly of adenomas. Long-term use of folate supplements seems to be of greater benefit than dietary intake and the effect is modulated by alcohol, methionine, and methylenetetrahydrofolate reductase polymorphisms.³⁰ Findings of this Review³⁰ also suggest an inverse association between folate intake and breast cancer in women who regularly consume alcohol.³⁰ Epidemiological evidence remains uncertain for the role of folate in cervical cancer prevention;³⁰ the results of two intervention trials^{31,32} on rates of cervical intraepithelial neoplasia regression or progression were negative.

In Canada, mandatory folic acid fortification was associated—in accord with previous epidemiological studies, for example, on brain—with a significant reduction in the incidence of neuroblastoma in children of mothers exposed to folic acid fortification.³³ A case-control study in Australia showed that folate supplementation in pregnancy reduced the risk of acute lymphoblastic leukaemia in the child.³⁴ Although there is increasing evidence that folate can prevent the development of new cancers in healthy people, there is also evidence that folate might enhance the progression of premalignant and malignant lesions.^{35–39}

Recommendations

The evidence of the benefit of folic acid in prevention of neural tube defects has since 1992, led many health organisations to issue recommendations for women to maintain a healthy diet and take folic acid supplements (0.4 mg daily; to prevent neural tube defect recurrence: 4 mg daily) when planning a pregnancy or throughout childbearing age.^{28,40} These recommendations might differ slightly: in Australia, for example, 0.5 mg folic acid daily is recommended.⁴¹ However, 0.4 mg per day was the quantity included in most multivitamin supplements associated with risk reduction in large observational studies.²⁸ Daly and colleagues⁴² estimated that delivery of 400 µg, 200 µg, or 100 µg daily via fortification would produce reductions in neural tube defect incidence of 47%, 41%, and 22%, respectively. A public-health campaign in northern China,⁴³ where prevalence was high (5–6 per 1000 births), resulted in a 79% reduction in defect risk, associated with a periconceptional daily intake of 0.4 mg folic acid as a supplement. In the southern region, where the prestudy neural tube defects prevalence was 1 per 1000 births, a lower, but still clinically significant reduction (41%), than that seen in the north was recorded. In an earlier Hungarian randomised clinical trial, a higher dose of 0.8 mg daily folic acid was used in combination with other vitamins.¹¹ The trial showed that the risk reduction of congenital anomalies (including neural tube defects) seemed to be greater than with folic acid alone.⁴⁴ The evidence for a protective effect is much stronger for folic acid supplements than for food folate, and an effect of natural folate on neural tube defects has yet to be shown.¹

Panel 2: Recommendations of the US Institute of Medicine¹

Adults: 0.4 mg/day of dietary folate equivalents
 Women capable of becoming pregnant: 0.4 mg/day of synthetic folic acid in addition to consuming food folate from a varied diet

For adults who cannot become pregnant, the US Institute of Medicine recommends 0.4 mg per day of dietary folate equivalents,^{1,45} whereas governments of European Union (EU) countries and of Switzerland recommend 0.2 mg per day.⁴⁶ The value of 0.4 mg is based on erythrocyte folate in conjunction with plasma homocysteine and folate concentrations.¹ The evidence for the role of folate in reducing the risk of vascular disease, cancer, and psychiatric and mental disorders was judged by the US Institute of Medicine not to be sufficient to use risk reduction of these conditions as a basis for setting recommendations.¹ The 0.4 mg per day of dietary folate equivalents recommended for adults are best provided by a healthy diet with plenty of vegetables and other foods rich in folate such as wholemeal products, which are independently associated with a reduced risk of cardiovascular disease and cancer.⁴⁷ The recommendations are not easily achieved, and people not willing to change their diet accordingly might benefit from foods fortified with dietary folate (eg, wheat germs) or synthetic folic acid to reach the recommendations (panel 2). Translation of these recommendations into practice, however, has proved difficult. The recommendations can be met by taking folic acid from foods fortified on a voluntary or mandatory basis, supplements, or both. An important issue is how effective are recommendations alone, or in combination with campaigns to increase knowledge and use of folic acid supplements periconceptionally among women.⁴⁸

Public awareness, knowledge, and appropriate use

In Western countries, most women of childbearing age or women who want to become pregnant have heard of folic acid; fewer women know that folic acid can prevent spina bifida and neural tube defects and an even lower percentage of women is aware of the fact that folic acid should be taken before pregnancy. For example, in Ireland in 2002, the corresponding percentages were 95%, 77%, and 62% respectively.⁴⁹ In the Netherlands in the same year, 50% of pregnant women knew of vitamins that might decrease the risk of birth defects.⁵⁰ In Spain in 2000, 52% of pregnant women were aware of the need to supplement their diet with folic acid at some time during pregnancy to prevent congenital malformation.⁵¹ And in the UK in that year, 76% of pregnant women had read information material before their pregnancy recommending the use of preconceptional folic acid.⁵² Knowledge is associated with a higher level of education, white race, wanted pregnancy, older age, prepregnancy consultation as to whether the

child has a neural tube defect, and a higher family income.^{50,53} Many countries undertook campaigns to increase knowledge and use of folic acid among women. In the Netherlands for example, a mass media campaign in 1995 achieved a considerable increase in awareness of the benefit of folic acid among pregnant women. However, the socioeconomic differences in knowledge remained unaffected; awareness seems to have stabilised at about 50% since 1996.^{50,54}

Despite high awareness and quite good knowledge of folic acid, in Ireland only 23% of pregnant women took folic acid periconceptionally.⁴⁹ The equivalent figure for the Netherlands⁵⁰ was 40%, and for Spain 7%.⁵¹ In a survey in Oslo, only 2% of immigrant women but 22% of Norwegians had used folic acid periconceptionally as recommended.⁵⁵ A study in England showed that only 48% of pregnant women took folic acid before 4 weeks of gestation; younger women and those who were more socioeconomically deprived were much less likely than older and well-off women to take folic acid during the critical periconceptional period.⁵⁶ In a systematic review of 52 studies, in about 20 (mainly western) countries between 1992 and 2001, the reported periconceptional supplement use ranged from 0.5% to 52%.⁵⁷ Predictors of reduced use were low educational level, unplanned pregnancy, young age, immigrant status, and lack of a partner.⁵⁷ The rate of unplanned pregnancy in 19 of these studies varied from 10% to 78%, with a median value of 42%.⁵⁷ In four studies examining the effect of mass media campaigns, the reported rates of periconceptional folic acid use increased substantially, but in no study was the rate after campaign greater than 50%.^{52,58-61}

Two analyses investigated the effectiveness, mainly in European countries, of recommendations in influencing trends in neural tube disorders.^{40,48} According to EUROCAT (European Concerted Action on Congenital Anomalies and Twins), a network of population-based congenital anomalies registries in Europe, in most European countries with periconceptional folic acid supplementation policy, there was almost no decline in total prevalence of neural tube defects including livebirths, stillbirths, and terminations of pregnancy from 1980 to 2002, whether a policy was in place by 1999 or not. In the UK and in Ireland, a 30% drop in overall prevalence was noted, but was difficult to distinguish from the pre-existing decline. Similar results were reported for the period 1992-98 in response to the neural tube defect intervention awareness campaign in South Carolina, USA.⁶²

Voluntary and mandatory fortification

Despite many public-health campaigns, a substantial proportion of women of reproductive age remain unaware of the need to take folic acid periconceptionally and an even higher proportion is not implementing the recommendations despite sufficient knowledge. Vulnerable groups are less educated individuals and young people, but also women who have unplanned

pregnancies. The only way to reach this group of women might be through fortification of foods with folic acid.⁶³ Moreover, in most countries without mandatory fortification, the general population is not consuming the recommended 0.4 mg of food folate per day.^{64–67}

National regulations for the fortification of foods intended for general consumption still vary greatly in the EU.^{68,69} Voluntary fortification has been practised for several years in various member states (UK, Ireland, Spain, Portugal, and Austria) as well as in Switzerland.^{68,70} In other member states (Denmark, Finland, and Sweden) voluntary fortification is either restricted or not allowed. In Ireland, the withdrawal of breakfast cereals fortified with folic acid for 12 weeks reduced red blood cell folate concentration in women by 111 nmol/L, thus impressively showing the possible effect of such a policy.⁷¹

In the USA since 1942, the Food and Drug Administration (FDA) has required enriched cereal grains to contain certain vitamins and minerals—ie, micronutrients removed by producing white flour were to be restored. Folic acid was not originally included, but the 1992 US Public Health Service folic acid recommendations suggested fortification. In 1996, the FDA issued regulations requiring that enriched grains (enriched flour, bread, rolls and buns, farina, corn grits, cornmeal, rice, and noodle, but not whole-grain products) be fortified by January, 1998.^{72–74}

In Australia and New Zealand, folic acid fortification of specified foods was first approved in 1995, and by 1999 more than 100 folate-fortified foods were available.⁷⁵ The prevalence of neural tube defects in Western Australia remained constant between 1966 and 1995, and fell thereafter by 29%.⁷⁶ The decrease coincided with folic acid promotion activities and the voluntary fortification of specified foods, but did not include indigenous infants. Thus, health promotion and voluntary fortification are not reaching all parts of the target population, and the 40–80% expected reduction in the neural tube defects rate has not been achieved in any country. In some countries, recommendations to consume folic acid supplements are therefore combined with the mandatory fortification of flour.

The level of folic acid fortification in the USA was set at 0.14 mg per 100 g of cereal grain product, and the average intake of folic acid in women of reproductive age was predicted to increase by about 100 µg per day.^{72–74} To receive the recommended 0.4 mg per day of synthetic folic acid per day women are recommended to additionally consume folic acid tablets.¹ Folic acid fortification improved folate status in the USA considerably. Data from the national health and nutrition examination surveys comparing 1999 with 1988–94 showed an increase of mean serum folate concentrations in women of reproductive age who did not use supplements, from 10.7 nmol/L to 28.6 nmol/L.^{28,77} Williams and colleagues⁷⁸ obtained population-based birth surveillance data for neural tube defects from 23 states and Puerto Rico, nine of which included prenatally

diagnosed defects. Compared with prefortification, the prevalence of spina bifida and anencephaly decreased by 31% and 16%, respectively, as ascertained from population-based surveillance systems (figure).^{78–83} However, the decrease of neural tube defects cannot be definitively attributed solely to fortification⁸⁴ because rates in the USA were declining even before fortification, as they were in many other western countries without mandatory fortification.⁸⁵

The increase in folic acid intake was larger than predicted and could have resulted from the fact that a number of enriched products contain higher concentrations of folic acid than required by law.^{86,87} In the Framingham Offspring Cohort Study, in participants (30–80 years of age) who did not use supplements, folic acid intake increased by a mean of 190 µg per day.⁸⁷ This increase is similar to that estimated by Quinlivan and colleagues⁸⁸ for the Framingham cohort (215 µg folic acid per day). A comparison of plasma and red blood cell folate concentrations from the same cohort before and after fortification indicated increases in plasma folate concentrations from 11 to 23 nmol/L⁸⁹ and red blood cell folate concentrations from 737 to 1020 nmol/L⁹⁰ in individuals not taking vitamin supplements. Fasting total homocysteine concentrations decreased by 7%.⁸⁹

After the USA decision, Canada recommended folic acid fortification in December, 1996 (0.15 mg folic acid per 100 g of flour, pasta, or cornmeal and 0.20 mg folic acid per 100 g of pasta), and it became mandatory in November, 1998. This intervention was expected to increase the average daily folic acid intake of women of childbearing age by about 100 µg per day.^{91,92} Women were advised to supplement their folic acid intake from fortified food with folic acid tablets to obtain the recommended 0.4 mg of synthetic folic acid daily.⁹³ The average additional dietary intake of folic acid due to fortification was 70 µg daily in women of 19–44 years of age in Newfoundland (1997–98 vs 2000–01).⁷⁹

A comparison of data from 1996–97 with 1998–2000 in Ontario, showed that the geometric mean red blood cell folate concentration rose from 527 nmol/L prefortification to 741 nmol/L postfortification in women aged 18–42 years.⁹³ The incidence of neural tube defects decreased by 48% in Ontario from 1995 to 1999.⁸⁰ In Quebec, de Wals and colleagues recorded a 32% reduction,⁸¹ and in Nova Scotia the defects rate went down by 54% after fortification.⁸² In Newfoundland, which previously had one of the highest rates in North America,⁹⁴ the rate fell by 78%.⁷⁹ The proportion of women taking a vitamin supplement containing folic acid went up from 17% to 28% in the same period.⁷⁹ The large reduction in rate in Newfoundland could be due, at least in part, to the fact that Newfoundland had higher background rates to begin with. All these surveys took the total of affected pregnancies (livebirths, stillbirths, and pregnancies terminated after a prenatal diagnosis of a neural tube defect) into account.

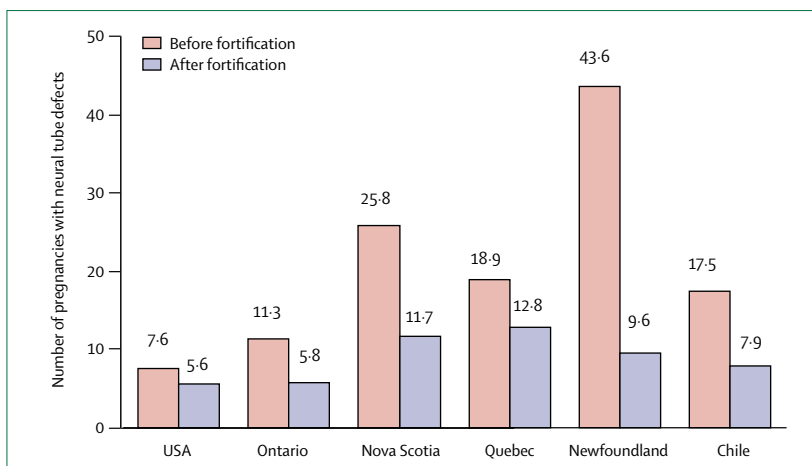


Figure: Rates of neural tube defects before and after fortification in regions with mandatory folic acid fortification

Numbers include livebirths and stillbirths, prenatally diagnosed cases, and elective abortions (Chile with livebirths and stillbirths only, USA with surveillance programmes with and without prenatal assessment).

The average dietary intake of folic acid due to fortification was 74 µg per day in people aged 65 years and older in Newfoundland, and there were increases in serum and red blood cell folate concentrations.⁷⁹ In Ontario, the mean serum folate was raised from 18.5 to 27.1 nmol/L in adults of mean age 57.4 years.⁹⁵ Neither the prevalence of orofacial clefts⁹⁶ nor the occurrence of trisomy 21⁹⁷ changed after food fortification. Similarly, no change in the rate of infant acute lymphoblastic leukaemia or hepatoblastoma was recorded. However, folic acid fortification was associated with a pronounced reduction in neuroblastoma in children.³²

In Chile, the fortification of wheat flour with 2.2 mg folic acid per kg has been mandatory since January, 2000. This policy was predicted to result in a mean additional consumption of 360 µg folic acid per day.⁹⁸ In a study with women of low income and of childbearing age, mean serum and red cell folate concentrations before fortification were 9.7 and 290 nmol/L, compared with 37.2 and 707 nmol/L after fortification, respectively. The median folic acid intake was 427 µg per day based on an estimated intake of 219 g of wheat flour after fortification. None of the study participants took folic acid supplements.⁹⁹

Chile showed a 31% decrease of neural tube defects between 2000 and 2001 (figure).⁷⁸⁻⁸³ There were no historical trends for the birth prevalence of anencephaly or of spina bifida. Induced abortion is illegal in Chile, but is nevertheless practised, and could perhaps be responsible for part of the reduction.^{83,98,100} In a group of elderly people in Santiago before fortification, folate deficiency (<6.8 nmol/L) was present in 1.8%, vitamin B12 deficiency (<165 pmol/L) in 27.6% and hyperhomocysteinaemia (>14 µmol/L) in 31% of the sample. 6 months later, mean serum folate rose from 16.2 nmol/L to 32.7 nmol/L, homocysteine decreased

from 12.95 µmol/L to 11.43 µmol/L and vitamin B12 concentrations were unchanged.¹⁰¹

In 2002, the UK Food Standards Agency decided against mandatory folic acid fortification, one reason being the potential for masking the diagnosis of a vitamin B12 deficiency.^{102,103} Similar reasons made the Dutch Health Council decide against mandatory fortification.¹⁰⁴ In other European countries like Switzerland⁶⁴ or Germany,¹⁰⁵ as well as countries such as Australia and New Zealand,¹⁰⁶ such a policy has been proposed to the government or is under assessment, or both. The UK Food Standards Agency decided in April, 2006, to reconsider mandatory fortification in addition to other options for improving the folate status of young women.¹⁰⁷

Safety of folic acid

Despite the noted beneficial effects of folic acid fortification on folate status and neural tube defects in countries that implemented either mandatory or voluntary fortification in addition to the promotion of supplement use, concern continues that folic acid might also have adverse effects.³⁵ Although folate is safe and almost free of toxicity,¹⁰⁸ concerns that folic acid fortification could mask symptoms of vitamin B12 deficiency and precipitate neurological complications have been raised.¹ Other examples of potential safety issues are interactions with drugs, hypersensitivity reactions, cancer promotion, and increase of twinning rate.^{108,109}

Vitamin B12 deficiency could affect up to 10–15% of the population over 60 years of age.¹ Importantly, however, many countries do not have population based prevalence data and vitamin B12 deficiency is often undiagnosed. The US Institute of Medicine¹ determined that there is suggestive, but not conclusive, evidence that folic acid, in addition to masking vitamin B12 deficiency, precipitates or exacerbates the neurological damage caused by vitamin B12 deficiency. This suggestion was based on three types of evidence. First, several human case reports showed onset or progression of neuropathy in vitamin B12-deficient patients receiving folic acid supplements. Second, studies in animals showed that neuropathy developed faster in those with vitamin B12 deficiency receiving folic acid than in controls. Third, a metabolic interaction between vitamin B12 and folate is well documented. On the basis of this evidence, the tolerable upper intake level for adults was set at 1 mg synthetic folic acid per day.¹

The amount of fortification chosen in the USA and Canada was estimated to provide on average 100 µg additional folic acid per day, with almost nobody receiving more than 1 mg.³⁴ In a study of elderly people in New Mexico, mandatory fortification with folic acid did not increase the likelihood of exceeding the upper intake level.¹¹⁰ In the USA, Canada, and Chile, folic acid fortification was associated with a reduction in the

prevalence of folate deficiency^{90,95,101} but not vitamin B12 insufficiency. Mills and colleagues¹¹¹ showed that the proportion of American patients with low vitamin B12 but without anaemia was 39% before fortification, and did not increase after fortification (38%). Accordingly, in a study of Canadian senior citizens, there were no significant changes in indices typical of vitamin B12 deficiencies, and no evidence of improved folate status masking haematological manifestations of vitamin B12.⁷⁹ Moreover, vitamin B12 deficiency is now diagnosed not by haematological data alone, but also by determination of serum vitamin B12, and possibly holotranscobalamin II, methylmalonic acid, and homocysteine concentrations.¹¹²

Although folate could prevent cancer in healthy people, it might also promote the progression of pre-malignant and malignant lesions. Low folate status and antifolate treatment, respectively, inhibit human tumour growth in these stages.^{35–39} The results of studies in animals suggest that the effect of folate on carcinogenesis is dependent on the stage of the carcinogenic process and the dose of folate tested;³⁶ folate deficiency inhibits, whereas folate supplementation promotes the progression of established tumours. However, folate deficiency in normal epithelial tissues seems to predispose them to neoplastic transformation, and modest doses of folate supplementation suppress, whereas supraphysiological amounts enhance, the development of tumours in normal tissues.³⁶ Long-term antiepileptic phenytoin therapy can result in folate deficiency, whereas supplementation with folic acid might lower serum phenytoin. Ray and colleagues,¹¹³ however, assessed all phenytoin drug concentrations measured in a large Canadian provincial laboratory between 1995 and 2003, and showed no appreciable change in values in relation to food fortification in Canada.¹¹³ Furthermore, evidence does not lend support to a substantial increase in seizure frequency in patients who are treated with oral folic acid.¹⁰⁹ A few case reports described hypersensitivity reactions to oral and parenteral folic acid, but most reactions were probably due to other components of the folic acid drug.^{109,114}

The results of a few studies^{115–117} have shown an increase in twinning rates associated with the use of multivitamin supplements containing folic acid. Twin pregnancies are at greater risk for infant morbidity and mortality.¹¹⁸ Postfortification twinning rates were not higher in the USA^{119–121} and similarly, in the extensive intervention study in China, folic acid supplements showed no effect.^{43,122} Positive associations may in part be explained by residual confounding of in-vitro fertilisation and ovarian stimulation, or by the effect of other vitamins in the multivitamins consumed,^{123–125} but the debate is not yet closed.¹²⁶

Furthermore, the hypothesis has been put forward that increased amounts of folic acid during the periconceptional period could lead to genetic selection by improving survival of embryos carrying the MTHFR 677C→T mutation, which could raise homocysteine

concentrations if folate intake is subsequently restricted in the child.^{127,128} Concerns about health risks that might be attributed to increasing intake of folic acid from fortified foods and increased use of dietary supplements cannot be definitively excluded, but—despite several years' experience of supplementation—definite adverse effects have not been observed. On the other hand, the monitoring of adverse effects might not have been comprehensive enough.¹²⁹

Public health implications

Despite public-health campaigns, knowledge about the proper periconceptional time to use folic acid supplements for the prevention of neural tube defects is not widespread in women and only a maximum of half of them are following the recommendations. Vulnerable groups are people of low educational status, young people, immigrants, and women with unplanned pregnancies. A substantial percentage of women still choose not to take the supplements even though they are aware of the beneficial effects. Reasons given in a campaign in the Netherlands¹³⁰ were being pregnant already and a dislike of taking drugs during pregnancy. 64% of the women in this campaign said that they would prefer to take folic acid in food rather than as a tablet. Both results were not associated with standard of education. Voluntary fortification improves the situation, but it does not reach all parts of the population. In countries with mandatory fortification of flour, folate and homocysteine status improved notably and neural tube defect rates fell by up to nearly 80%. Nevertheless, many countries do not choose mandatory folic acid fortification, in part because expected additional benefits such as the prevention of other major birth defects, cardiovascular diseases, and cancer are not yet scientifically proven in clinical trials, and in part because of feared health risks. In addition to these factors, the issue of choice plays an important part.

To ensure that all women capable of becoming pregnant have an adequate periconceptional intake of folic acid, each country should choose the policy best suited for the circumstances.¹³¹ In the absence of mandatory fortification on a sufficient level, national campaigns to increase knowledge and use of folic acid among women should be intensified and adequately funded. Special attention should be paid to factors such as language, cultural barriers, and illiteracy.⁵⁷ An alternative could be adding the folic acid supplementation recommendations to contraceptive packages (of intrauterine devices, pills etc) and recommending women to start folic acid supplementation after stopping their contraception. Access to inexpensive folic acid supplements might also be of importance.⁵⁷ Obstetricians, paediatricians, and general practitioners can play an important part in informing and motivating women to take folic acid supplements periconceptionally.⁵⁰

Women report that health-care professionals are the most effective means of communicating the importance

of folic acid,¹³² followed by television and advertising. Perhaps a necessary strategy is to re-emphasise knowledge of the correct time and dosage of folic acid supplementation¹³³ and the need to start antenatal care before conception¹³⁴ among health-care providers. A folic acid dispenser in the shape of an artificial sweetener box could help to make folic acid supplements part of ordinary life, and might be more acceptable for women who do not like to take drugs. Another public-health approach to improve knowledge and compliance could be to engage important and trustworthy people as godfathers or godmothers of promotion programmes. Health messages from celebrities about, for example, cancer screening,¹³⁵ avoiding tobacco,¹³⁶ or high-risk sexual behaviours¹³⁷ are becoming increasingly common with some promising results^{135,137} also in lower social classes and minority groups. In Switzerland for example, Olympic medals skier Maria Walliser is acting as a godmother in a folic acid campaign.

In Europe,⁵⁶ on average, more than 40% of pregnancies are unplanned, more effective prevention of neural tube defects could be achieved by introducing fortification of a staple food with folic acid. This approach could also reduce socioeconomic inequalities in prevalence. In countries that decide to follow this route, a detailed plan for assessment not only of the effect but also of the safety of the intervention should be worked out beforehand. Assuring adequate funding and assignment of clear responsibilities is also of major importance.¹²⁹ Careful monitoring—and if necessary, policy adaptation—ensures that potential unintended consequences are detected at an early stage. As already mentioned, definite adverse effects of food fortification—despite almost 10 years of mandatory fortification—have not been noted until now.

Solving the difficulty of choice is more complex. With mandatory fortification, everybody has to consume fortified products even if they prefer not to, meaning that a decision is made for an entire population without asking for individual informed consent.^{35,74} Provision of an unfortified version of a fortified staple food (eg, wholegrain wheat flour products in the USA) is reasonably easy; but choice seems to encompass much more than just the choice of another kind of bread. Food fortification is sometimes thought of as patronising and is associated with vague fears of medicalisation of food, not believing in scientific evidence, and not trusting scientists, politicians, and other decision-makers. Scientific evidence provided by careful monitoring and assessment will not be sufficient to calm these fears. Promotion of folic acid fortification programmes by celebrities might be useful in this context, but the goal would rather be to inform than to convince.¹³⁵

Conclusions

In countries choosing mandatory fortification with folic acid, careful assessment of beneficial as well as potential negative health effects is of prime importance. In countries deciding against mandatory fortification,

promotion and funding of research on additional effective means to improve folic acid supplement use is essential. At present, there exist only a few new strategies, which are not yet part of comprehensive folic acid campaigns worldwide. Thus, not only careful monitoring and research in relation to safety issues of folic acid fortification is required. Equal emphasis should be laid on the research and assessment of new creative public-health strategies to improve folic acid supplementation in the prevention of neural tube defects.

Conflict of interest statement

We declare that we have no conflict of interest.

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